PhRMA

0377 '96

June 22, 1998

Ms. Minnie Baylor-Henry
Director, Drug Marketing, Advertising
and Communications Division
Office of Drug Evaluation 1, CDER
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: Promotional Use of Health Care Economic Information - Recommended Approach for Implementing FDAMA~114

Dear Ms. Baylor-Henry:

We are writing on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA) to provide industry input on Section 114 of the FDA Modernization Act of 1997 (FDAMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies; this year alone our member companies are expected to invest over $20 billion in discovering and developing n-ew medicines.

0378 '96 JUN 23 P2:11

As you know, FDAMA~114 amends Section 502(a) of the Food, Drug, and Cosmetic Act to allow health care economic information (HCEI) that directly relates to an approved indication to be provided to formulary committees or similar entities, so long as such information is based on "competent and reliable scientific evidence." This provision, which took effect February 19 of this year, was intended by Congress to provide significant new authority for the provision of HCEI to managed care or other similar health care providers with drug selection responsibility.

PhRMA's Pharmacoeconomic Work Group, with the assistance of the PhRMA Health Outcomes Work Group (HOWG), prepared the attached recommended Guidance For Industry. Considerable professional experience in the HCEI outcomes discipline was brought together in this effort to assist FDA in implementing this important new provision, and also to assist our members in utilizing it. The Pharmacoeconomic Work Group is available at your convenience to discuss this recommended approach. We hope that you and

98D-0468 C1

others at FDA, and interested members of the public, find this input useful, and that the Agency makes it widely available.

Sincerely yours,

Timothy R. Franson, M.D.

Timothy R. Franson, M.D.
Vice President, Clinical Research and
Regulatory Affairs – U. S., Eli Lilly and Company
Chair, PhRMA Pharmacoeconomic Work Group
3171277-1324

Jean-Paul Gagnon, PhD

Jean-Paul Gagnon, Ph.D
Director, Health Outcomes Research Policy
Hoechst Marion Roussel
Chair, PhRMA HOWG

Russel A Bantham

Russel A. Bantham
Senior Vice President and General Counsel
PhRMA

cc: Jane Axelrad, Associate Director for Policy, CDER/FDA

GUIDANCE FOR INDUSTRY[1]

Promotional Use of Health Care Economic Information

Under Section 114 of the

Food and Drug Modernization Act

I. Introduction.

Under section 502(a) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), a drug is deemed to be misbranded "if its labeling is false or misleading in any particular." (21 U.S.C. § 352(a)). Section 114 of the Food and Drug Administration Modernization Act ("FDAMA") (PL 105-115) amends section 502(a) to specify "health care economic information provided to a formulary committee, or other similar entity, in the course of the committee or the entity carrying out its responsibilities for the selection of drugs for managed care or other similar organizations, shall not be considered to be false or misleading under this paragraph if the health

[1]This guidance has been prepared by FDA's Division of Drug Marketing, Advertising and Communication. This guidance represents the agency's current thinking on promotional use of health care economic information. It does not create or confer any rights for or on any person and does not operate to bind FDA or the industry. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

care economic information directly relates to an indication approved under section 505 or under section 351 (a) of the Public Health Service Act for such drug and is based on competent and reliable scientific evidence."

Although section 114 of the FDAMA changes significantly the standard for the Food and Drug Administration's (FDA) review of promotional materials that comprise health care economic information ("HCEI"), it does not affect other, existing regulatory standards outside that context. The new standard affects only FDA's review of promotional materials under section 502(a) of the FFDCA. It does not change established rules and FDA policies governing dissemination of information on drug prices (e.g., 21 C.F.R. § **200.200),** promotional use of other information about a drug or the dissemination of information, including HCEI, in a non-promotional context, such as manufacturer responses to unsolicited requests for information about a drug or industry-supported scientific and educational activities. See "Final Guidance on Industry-Supported Scientific and Educational Activities." 62 Fed. Reg. 64074 (December 3, 1997). This also does not affect the agency's current guidances on dissemination by drug manufacturers, of certain reprints of journal articles and reference texts (medical textbooks and compendia) which contain information concerning FDA-approved products that may not be consistent with approved labeling for the products, entitled "Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data," and "Guidance for Industry Funded Dissemination of Reference Texts." 61 Fed. Reg. 52800 (October 8, 1996).

The agency is providing this guidance to describe the agency's policy for reviewing promotional materials comprising HCEI under section 114 of the FDAMA. This

guidance seeks to clarify the agency's interpretation of several terms included in section 114, to describe the process for submission and review of promotional materials comprising HCEI, and to describe the criteria FDA will use to determine whether or not promotional materials comprising HCEI meet the competent and reliable scientific evidence standard for substantiation.

II. Background.

A. History of FDA Regulation of Pharmacoeconomic Information.

Increasingly, HCEI is becoming an important part of the information used by managed care organizations, integrated delivery systems, and other organizations to make drug selection decisions. At the October 1995 FDA public hearing "Pharmaceutical Marketing and Information Exchange in Managed Care Environments," several representatives from managed care pharmacy backgrounds described the need for health care economic information and their use of those data. Richard Jay, Pharm. D., Vice President Corporate Pharmacy Services, FHP, Inc. (a mixed group-independent practice association model managed care organization with nearly 2 million members) stated:

> [A]ccess to valuable and meaningful outcomes, cost-effectiveness information spanning entire episodes of medical care could prove extremely valuable. Such information provided by a pharmaceutical company could lead to improvement in quality and reduced cost for a managed care organization, as well as the health care industry in general.
>
> ...
>
> Regardless of what is ultimately decided with respect to the way the kinds of information in question are communicated, it is incumbent upon the managed care organization itself, or other

recipient of the information to develop systems internally, structures and processes by which they can evaluate this information internally, so that they can come to their own meaningful conclusions on drug therapy decisions.

James Lang at ValueRx, a pharmacy benefit management company, summarized the problems his organization faces in making decisions about drug therapy:

> The types of information we put before the [Pharmacy and Therapeutics Committee] and evaluate internally include Phase 3 and Phase 4 and post-marketing clinical trials; manufacturer–supplied information; when available, academic clinical trials; medical texts; drug compendia; articles from peer-reviewed and scientific publications; presentations and proceedings from medical meetings; and, if available, national benchmarks and published guidelines.
>
> The problem with most of this information, from our perspective, is that the clinical trial data in particular is of an artificial environment and not a real life situation, which makes it very difficult to make decisions that impact real life utilization of the drugs; and including strict inclusion and exclusion criteria that don't really categorize or adequately describe the population that these drugs are going to be used in; and, in particular, no comprehensive pharmacoeconomic data is included.
>
> The types of pharmacoeconomic –the situation in our environment for pharmacoeconomic evaluation is really very, very limited data is available, considering the broad number of categories that need to be evaluated. The reality of the fact is that managed care makes pharmacoeconomic decisions on a daily basis, and because the data is unavailable, oftentimes treat this in a cost minimization mode where they treat most drugs as if they were equivalent, which may or may not be the case.
>
> The types of information that we really need are more realistically designed outcome studies, with economic data included and involving a broader category of costs and scope of costs, and then particularly outcome for all patients, and the cost of treatment failures and the cost of that therapy that is required because of that treatment failure.

As a consequence, pharmaceutical companies are conducting studies and analyses to provide those data. According to the Senate Report accompanying FDAMA, "Health economic information about approved 'on label' uses is needed by managed care experts and other health care providers responsible for evaluating the benefits, other consequences, and costs of competing therapies. Health care providers also rely on companies to conduct studies in the providers' own or comparable representative populations to help the providers predict the specific benefits and costs of FDA-approved products for their particular organizations." S. Rep. No. 105-43, at 42-43 (July 1, 1997), This citation accords with the House Report, which states: "The type of health care economic information that can be provided pursuant to this section is that which is directly related to an approved labeled indication." (H.R. Rep. No. (105-3 10, at pp. 65-66).

As pharmaceutical companies expanded their use of HCEI, by the mid- 1990s FDA's role as a regulator became an important issue. The agency began considering how to apply economic information to the statutory requirement under section 502(a) that information not be false or misleading. The law clearly permitted the assignment of costs to clinical outcomes demonstrated by adequate and well controlled clinical trials. But the agency also had to assess whether the statute permitted a whole range of economic approaches to evaluating resource utilization findings shown in observational studies to flow from outcomes that are demonstrated by adequate and well controlled trials.

To address these issues, in March 1995, FDA's Division of Drug Marketing, Advertising and Communications released its Draft Principles for the Review of Pharmacoeconomics at a public workshop on comparative effectiveness, safety, and cost-effectiveness, In October 1995, FDA held the above-referenced public hearing as its "first formal step in developing policies to assure that health care decision makers have access to the information they need to make the best possible decisions and that the public health is protected at the same time by assuring that false or misleading promotional information does not become the basis for medical decision making." (Statement from Janet Woodcock, M.D., Director, Center for Drugs Evaluation and Research) In November of 1996, a Public Health Service Task Force presented its views at a workshop on Cost Effectiveness in Health and Medicine. The internal FDA discussions stimulated by these public meetings continued during 1997, but it soon became clear that Congress might address the issue in legislation.

B. Congressional Action.

Congress did address the issue in section 114 of FDAMA. In drafting that section, the Senate noted the importance of HCEI, and expressed the view that the flow of such information should increase. S. Rep. No. 105-43, at 42-43. In particular, the Senate noted that the "two clinical trial" substantiation standard inhibited the sharing of useful information. Id. The Senate Report states:

> The committee believes that the FDA should allow companies to share health economic information about approved "on label" uses for products under the same standard applied to over-the-

> counter drugs and other products. The agency currently requires these claims—which differ from efficacy claims-to be subjected to two clinical trials. The agency on several occasions conceded that this standard is inappropriate for such claims and agreed that it should be modified to a more appropriate standard.
>
> …
>
> The FDA should not unduly impede the flow of that information to experts who need it for patient and health plan decisions. Undue restrictions on the ability of companies to make competent and reliable claims on the basis of cost, effectiveness, or safety of approved uses of products interfere with the public health by encouraging the sale and use of needlessly expensive products.

Id. Rather than simply change that standard across the board, however, Congress took a different approach.

For certain types of messages provided to certain audiences, as described more filly below, Congress sought to impose a more flexible and less restrictive substantiation standard consistent with the 'directly related to an approved labeled indication' language in the House Report. To achieve the greater flow of information that Congress desired, Congress adopted by reference the standard of substantiation employed by the Federal Trade Commission ("FTC") for over-the-counter pharmaceutical marketing. See S. Rep. No. 105-43, at 3-4 and H.R. Rep. No. 105-310, at 65-67. To define the types of information and permitted audience, Congress: (1) limited the type of information that could be disseminated under the competent and reliable scientific evidence standard to HCEI directly related to an approved labeled indication, and (2) limited the audience to whom information could be disseminated under that standard to formulary committees or similar entities responsible for selecting drugs for managed care or other similar organizations. 21 U.S.C. 352(a). That audience comprises those who have

more expertise in evaluating drug therapies than patients or health care providers not involved with those activities. See, S. Rep. No. 105-43, at 3-4 ; H.R. Rep. No. 105-310, at 65-67. These limitations on the dissemination of information under section 114 provide safeguards for the more flexible and less restrictive evidence standard imposed by that section.

The analysis of the impact of section 114 starts with the premise that Congress intended to increase the flow of information between manufacturers and managed care decision-makers with respect to health care economic analyses. See, S. Rep. No. 105-43, at 42-43; H.R. Rep. No. 105-310, at 65-67. As a consequence, the promotional activity now permitted under Section 114 must go beyond previous FDA policy that permitted promotional dissemination of HCEI which simply assigns dollar values (or other cost measures) to outcomes proved by adequate and well controlled trials, to encompass outcomes and costs collected outside of adequate and well controlled trials, but still directly related to the labeled indication.

We also start with the rule of **statutory** construction that the Act must be read to give meaning to all parts of the statute including the restrictions imposed on the use of HCEI (i.e., the scope of that term, the limits on the permitted audience, and the requirement in the House Report that the information be directly related to an approved labeled indication). Reading those restrictions in tandem with the goal of increasing the flow of information leads to the inference that the substantiation standard Congress borrowed from FTC was intended to be less restrictive than the prior standard that applied to all information conveyed in promotional labeling and advertising for prescription drugs, including HCEI. Such a reading gives meaning

to the statutory restrictions because it means that Congress placed parameters around the information that would be subject to this new, less restrictive standard.

Congress recognized that HCEI inherently includes comparative clinical information and other extensions from data based on adequate and well controlled clinical trials using reasonable assumptions about health care economic consequences. In the House Report, five examples are provided: rheumatoid arthritis; heart failure, Type I diabetes; osteoporosis; and meningitis associated with haemophilus b influenza vaccination. See, H.R. Rep. No. 105-310, at 65-67. Given (1) the goal of Congress to increase the flow of information from pharmaceutical companies to managed care entities, (2) the restrictions that Congress placed on the process for providing that information and (3) the fact that prior law already permitted the mere assignment of costs to clinical outcomes proven through substantial evidence, Congress apparently intended to apply the less restrictive substantiation standard to the various elements of HCEI directly related to an approved labeled indication, including the comparative clinical information and other extensions beyond data based on adequate and well controlled clinical trials. To clarify that, the House Report explains that "Incorporated into economic consequences are the costs of health outcomes. Data about health outcomes associated with the use of a drug, other treatments, or no treatment are therefore incorporated into the economic analysis." H.R. Rep. No. 105-310, at 65-67. Thus, Section 114 allows dissemination of those data-even where the substantiation for the clinical data underlying the HCEI may involve methods other than adequate and well-controlled trials-as long as the data are (1) part of an economic analysis supported by competent and reliable scientific evidence, (2) directly related to an approved indication and (3) disseminated under the other limitations noted above.

c. FDA Reviews of Promotional Materials.

Since Congress only sought to address the use of HCEI in the promotional context, in section 114 Congress left undisturbed other rules and regulatory policies that FDA has developed for such information issues as industry support of scientific and educational symposia and unsolicited requests for product information. Because section 114 was effective on February 19, 1998, without the need for implementing regulations, since that time FDA administered the new provision through its process for collecting promotional labeling and advertising at the time of first use for drug products subject to a new drug application. When FDA examines promotional materials it receives, the agency must distinguish between HCEI and all other types of promotional materials. The agency thus applies the competent and reliable scientific evidence to HCEI under Section 114, and the substantial evidence test to most other types of information.

D. FDA's New Standard for Substantiating HCEI.

1. FTC Origins of the Standard.

For information that meets the definition of HCEI and satisfies the other limitations specified in the statute, to encourage pharmaceutical companies to share more information than they have been able to in the past, section 114 requires that the information be

substantiated by competent and reliable scientific evidence as that term is used by the FTC. According to the Senate Report:

> This provision differentiates between clinical claims and economic claims. Clinical claims would continue to be governed by the evidence standard in the Act. Economic claims would be governed by the "competent and reliable scientific evidence standard used by the Federal Trade Commission, drawing from available evidence in the relevant economic fields of science."

S. Rep. No. 105-43, at 42-43, Thus, Congress explicitly borrowed the FTC standard of substantiation, and applied it to HCEI regulated by FDA. The House Report more specifically explains:

> The standard of competent and reliable scientific evidence (49 Fed, Reg. 3099) (August 2, 1984)) supporting health care economic information provided under this subsection takes into account the current scientific standards for assessing the various types of data and analyses that underlie such information. Thus, the nature of the evidence required to support various components of health care economic analyses depends on which component of the analysis is involved. For example, the methods for establishing the economic<, costs and consequences used to construct the health care economic information would be assessed using standards widely accepted by economic experts. The methods used in establishing the clinical outcome assumptions used to construct the health care economic analysis would be evaluated using standards widely accepted by experts familiar with evaluating the merits of clinical assessments. In addition, the evidence needed could be affected by other pertinent factors.

H.R. Rep. No. 105-310, at 65-67.

As already noted, Section 114 incorporates the FTC standard using the phrase "competent and reliable scientific evidence." When enacting the new FDA standard, Congress borrowed that FTC phrase, including the word "scientific," defining that agency's standard for

substantiation of claims involving scientific data. For example, FTC used this exact standard in its regulation covering environmental claims in 16 C.F.R $260.5. In describing its evidential standard for advertising general goods and services such as clothing and toys, FTC officials typically use the phrase "competent and reliable evidence". When talking about goods such as pharmaceuticals that implicate science, FTC officials typically use the more specific phrase of "competent and reliable scientific evidence."2

2. Meaning of the Standard in FTC Orders.

In recent years, the FTC's Orders in most drug cases define the phrase "competent and reliable scientific evidence" as "tests, analysis, research, studies or other

---

[2]While the following methodology has its limitations, to determine what phrase FTC uses in its orders to reference its substantiation standard for drugs, one could search in the LEXIS - Trade - FTC computer database. This database contains all FTC orders since 1950. Court decisions are not included. We tested to find out which of the following phrases-- "competent and reliable scientific evidence" and "competent and reliable evidence''—FTC uses more often in the drug context. The following are the search results as of 2/10/98.

Search 1:	("competent" within one word of "reliable" within one word of "scientific") and (drug or pharmaceutical)
Results:	297 FTC orders were responsive.
Notes:	We have checked a good sample of the responsive cases, and this search definitely picks up the phrase "competent and reliable scientific evidence." It also picks up any mention of the "Food and Drug Administration", so it is possible that not all of the responsive cases concern drugs.
Search 2	("competent" within one word of "reliable" within one word of "evidence") and (drug or pharmaceutical)
Results:	110 FTC orders were responsive
Notes:	This search does pick up the phrase "competent and reliable evidence." It also picks up cases in which both phrases appear.

evidence based on the expertise of professionals in the relevant area that has been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted by others in the profession to yield accurate and reliable results." E.g. *Herbal Ecstasy* (OTC psychotropic drug) - In re Global World Media Coloration, 1997 FTCLexis314 (Oct. 17, 1997); *Bonebuilder* (OTC calcium supplement) -In re Metagenics, Inc., 1997 FTC *Lexis 313* (Oct. *31,* 1997); *Venoflash* (treatment for circulatory system blockage, varicose veins and hemorrhoids) - In re Efficient Labs, Inc., 1997 FTC *Lexis 303* (Sept. **12, 1997);** *Nutriol* (OTC topical hair treatment) - In re Nuskin International, Inc., 1994 FTC *Lexis 322* (April 1, 1994); *Y-Bron* (anti-impotency drug) -In re Michael S. Levey, 1993 FTC *Lexis 240* (Sept. *23, 1993);* FTC also has applied the same definition in a fairly large number of cases involving weight loss products. *NutraTrim -In* re Kave Elahie d/b/a M.E.K. International, 1997 FTC *Lexis 308* (Sept. 19, *1997); Superformula Reductora* - In re Rogerio Monteiro, 1997 FTC *Lexis 307* (Sept. 12, *1997); Svelt-patch -In* re 2943174 Canada, Inc., d/b/a United Research Center. Inc., 1997 FTC *Lexis* 163 (June 16, 1997); *Fat Burners -In* re Amerifit, Inc., 1997 FTC *Lexis 128* (June 16, 1997); *SeQuester -In* re KCD Holdings, Inc., 1996 FTC *Lexis 737* (Dec. 18, 1996); *Ensure* products - In re Abbott Laboratories, 1996 FTC *Lexis 707 (Dec. 23,* 1996); *Nu-Day Diet Program* - In re Nu-Day Enterprises, Inc., 1992 FTC *Lexis 105* (Apr. 22, 1992).

3. Meaning of the Standard in FTC Statements.

According to the FTC's policy statement on advertising substantiation (49 Fed. Reg. 30999 (August 2, 1984)) expressly referenced in the House Report on FDAMA (H. R. Rep. No. 105-310, at 65-67), FTC's standard for prior substantiation can be summarized as follows:

> Many ads contain express or implied statements regarding the amount of support the advertiser has for the product claim, When the substantiation claimed is express (e.g., "tests prove", "doctors recommend", and "studies show"), the Commission expects the firm to have at least the advertised level of substantiation. Of course, an ad may imply more substantiation than it expressly claims or may imply to consumers that the firm has a certain type of support; in such cases, the advertiser must possess the amount and type of substantiation the ad actually communicates to consumers.
>
> Absent an express or implied reference to a certain level of support, and absent other evidence indicating what consumer expectations would be, the Commission assumes that consumers expect a "reasonable basis" for claims. The Commission's determination of what constitutes a reasonable basis depends, as it does in an unfairness analysis, on a number of factors relevant to the benefits and costs of substantiating a particular claim. These factors include: the type of claim, the product, the consequences of a false claim, the benefits of a truthful claim, the cost of developing substantiation for the claim, and the amount of substantiation experts in the field believe is reasonable. Extrinsic evidence, such as expert testimony or consumer surveys, is useful to determine what level of substantiation consumers expect to support a particular product claim and the adequacy of evidence an advertiser possesses.

This approach to deciding the level of substantiation required necessitates a new approach by FDA for review of promotional materials involving HCEI. Rather than prescribing the specific methods by which HCEI must be obtained, the FTC standard incorporated into

section 114 is a flexible one that allows for variation in the types of evidence that are adequate to meet the statutory burden depending upon the facts and circumstances of each case. The factors FTC lists in its notice are important to the FTC standard, and involve areas that FDA has not previously considered when determining whether or not there is substantial evidence to support promotional claims, For example, the FTC's explanation of its standard expressly identifies the cost of substantiating a claim as a factor to be weighed against the benefit of the information to the audience,

In the context of HCEI, the burden to conduct additional controlled clinical trials—beyond those adequate and well-controlled trials already conducted to support the labeled indication—to demonstrate economic endpoints may be substantial. Economic endpoints generally show greater variability than efficacy endpoints; therefore studies to obtain HCEI often need to enroll larger numbers of patients to obtain significant findings. Important economic endpoints often require substantial time periods for follow up; therefore, studies to obtain HCEI may continue for long periods of time before results can be obtained. In addition, once controlled trials are completed showing the efficacy of a therapy, it maybe more difficult to obtain provider or patient consent to participate in randomized controlled trials.

Other factors included in the competent and reliable scientific evidence standard as described in the FTC notice involve the nature of the claim and how the information is to be used. To an extent, Congress already dealt with these issues in defining the scope of section 114, By limiting the information to HCEI that reflects an approved labeled indication and by limiting the audience to those selecting drugs for groups, Congress limited the risk that insufficient

clinical information would be used as a basis for specific treatment decisions. In addition to those statutory parameters, the competent and reliable scientific evidence standard specifically requires balancing the benefits of a truthful claim with the consequences of a false claim under the facts of each case. Thus, in the context of HCEI, a person weighing those factors must consider that (1) HCEI is limited to approved labeled indications (i.e. those for which safety and effectiveness have been proven by substantial evidence), and (2) in order for an economic claim to drive a health care decision, the clinical factors generally need to be acceptable on their own merits.

In the FTC's Federal Register notice, the FTC also explains how it determines which claims the promotional material makes. Promotional materials make express claims that the materials spell out, but they also might imply claims without stating them expressly. According to the FTC: "One issue the Commission examined was substantiation for implied claims. Although firms are unlikely to possess substantiation for implied claims they do not believe the ad makes, they should generally be aware of reasonable interpretations and will be expected to have prior substantiation for such claims. The Commission will take care to assure that it only challenges reasonable interpretations of advertising claims." 42 Fed. Reg. at 30,999. This is an important element of FTC's standard.

Significantly, FTC encourages comparisons in advertising to facilitate competition and ensure that the market place receives the information that it needs to make choices. Indeed, the FTC prohibits standards of substantiation adopted by industry associations that require higher substantiation for comparative claims than for unilateral claims. 16 C.F.R §

14.15. Thus, in transferring the FTC standard to FDA, FDA will be careful to ensure that the application of the competent and reliable standard facilitates —rather than discourages — comparative claims .

4. Meaning of the Standard in FTC's Comments on Managed Care Promotion.

The FTC has interpreted the competent and reliable scientific evidence standard in the context of promotion of prescription drugs to managed care customers on the basis of "economic claims." In a comment letter dated January 16, 1996 to FDA, FTC explained how it regulates economic claims relating to pharmaceuticals. According to the comment letter, "[A] number of factors influence the type of evidence required for substantiation of advertising claims under the FTC's substantiation policy. One important factor is the relevant professional standards appropriate to judge the evidentiary support for the type of claim at issue. Under this approach, the required level of substantiation for economic claims for pharmaceutical products, such as cost-benefit or cost-effectiveness claims, would depend on the content of the claim made."

In its comment, FTC offered specific advice on the types of data required to substantiate these economic drug claims:

> A variety of field and other types of data are used in assessing economic questions, including cost-benefit and cost-effectiveness questions. While controlled trial data are often

desirable for assessing certain types of questions, economic practice would not necessarily require such data for assessments of cost-benefit issues in general or of health issues in particular. In part, this reflects the high cost and long time lag necessary for collecting this type of data in many circumstances. It also reflects the fact that actual use experience can deviate from the experience observed in controlled trials due to potential biases in controlled trial data and to the different conditions in actual doctor-patient interactions, as described below,

For economic questions, the literature suggests that differences in the outcomes from controlled trials and actual experience can be important in predicting behavior and in estimating the costs and benefits of various health care options. For instance, in the pharmaceutical context, side effect or convenience differences between drugs can significantly affect the likelihood that physicians and consumers will stay with a particular drug treatment. Controlled trials, in which compliance is tightly restricted for the duration of the trial in order to get a better measure of efficacy, can give substantially different results than would be found in a clinical setting, where continuation of treatment is more likely to vary with characteristics of the drug. Similarly, the literature suggests that behavioral results can be substantially affected by randomization bias, a type of selection bias that occurs when random assignment causes the type of person participating in the trial to differ from the type of person who would receive the drug in the normal clinical setting. As a result, controlled trial data can sometimes predict actual clinical implementation poorly. In this type of situation, experience with the drug in a field setting may substantially add to the available knowledge based on trial data, or may actually give superior information about economic and effectiveness issues in actual practice to that provided by a controlled trial. Such data may also raise questions about the results from controlled trials.

At the end of its comment, FTC offered as its advice to FDA the notion that insistence on substantial evidence would preclude the use of important, truthful data. In particular, FTC urged:

Depending on how it is interpreted and applied, the FDA statement in the Federal Register notice that all 'effectiveness' elements of cost-effectiveness claims must be based on adequate and well-controlled studies" could result in the prohibition of many truthful, non-deceptive claims describing the cost-effectiveness or cost-benefit characteristics of pharmaceutical products in actual treatment settings. Claims substantiated by competent and reliable epidemiologic, administrative, or other clinical data would appear to be prohibited under this standard. Claims based on shared data from HMOS or other insurers nationwide would also appear to be excluded.

If an economic claim clearly discloses the nature of the result and the data on which it is based, and the data are competent and reliable, it could provide truthful, non-misleading information to professional and insurance customers. Accurate economic claims based on actual experiences in the field, particularly when directed to these types of audiences, do not appear to us to be inherently deceptive or otherwise misleading.

Thus, FDA may wish to consider a more flexible substantiation standard for economic claims for pharmaceutical products, for instance, one requiring "competent and reliable evidence" to support the claim that is made, without an *a priori* specification as to the type of evidence required. Such a reasonable basis standard could be effective in limiting deceptive claims without having the undesirable effect of preventing truthful economic claims. In some instances, controlled trial testing may be the appropriate type of substantiation for a particular type of economic claim, as when an efficacy claim is included, but in other circumstances other types of evidence might constitute appropriate substantiation.

E. Limitations on the Scope of Section 114.

1. Directly Related to an Approved Indication.

In addition to fitting within the parameters of the term HCEI, section 114 further limits the types of messages that would qualify for this special treatment to include only

information that is directly related to an indication approved by FDA. for inclusion in the drug's labeling. In particular, amended section 502(a) states that HCEI "shall not be considered to be false or misleading under this paragraph if the health care economic information directly relates to an indication approved under section 505 or under section 351(a) of the Public Health Service Act for such drug... ." It is instructive that Congress chose to emphasize the concept of labeled indication rather than the broader term "use." Although managed care decision-makers may commonly consider the inclusion on formulary of off-label uses of approved drugs, section 114 does not authorize dissemination by manufacturers of promotional information related to those uses even under the more liberal evidence burden of that section. Section 114 is limited to approved indications--i.e. those uses of an approved drug directly related to an indication approved under section 505, or section 351(a) of the Public Health Service Act.

2. The Permitted Audience.

The second limitation to the reach of section 114 involves the audience to whom manufacturers are permitted to disseminate the information. Congress made the legislative finding of fact that the professionals falling within the categories outlined in the statute have adequate expertise and experience to understand and make appropriate use of information that satisfies the competent and reliable scientific evidence test. H.R. Rep. No. 105-310, at 65-67. Although specific procedures may vary from one organization to another, those entities generally have established policies and procedures for evaluating information on drug therapies including HCEI.

Section 502(a) provides, in part, that "health care economic information [may be] provided to a formulary committee, or other similar entity, in the course of the committee or the entity carrying out its responsibilities for the selection of drugs for managed care or other similar organizations." Explaining Congressional intent with regard to that limitation, the House Report notes that:

> The purpose of section 10 is to make it possible for drug companies to provide information about the economic consequences of the use of their products to parties that are charged with making medical product selection decisions for managed care or similar organizations. Such parties include formulary committees, drug information centers, and other multidisciplinary committees within health care organizations that review scientific studies and technology assessments and recommend drug acquisition and treatment guidelines. The provision is limited to analyses provided to such entities because such entities are constituted to consider this type of information through a deliberative process and are expected to have the appropriate range of expertise to interpret health care economic information presented to them to inform their decision-making process, and to distinguish facts from assumptions. This limitation is important because it will ensure that the information is presented only to parties who have established procedures and skills to interpret the methods and limitations of economic studies. The provision is not intended to permit manufacturers to provide such health care economic information to medical practitioners who are making individual patient prescribing decisions nor is it intended to permit the provision of such information in the context of medical education.

H.R. Rep. No. 105-310, at 65-67.

In limiting the audiences that could qualify for this special treatment, section 114 adopts the FTC approach to determining required levels of substantiation based upon the target audience. Audience plays an important role in the substantiation required under the FTC's competent and reliable scientific evidence standard. The FTC commented on the importance of the audience considerations in its letter to FDA on promotion to managed care. According to FTC, "As noted in the FDA's *Federal Register* notice, many economic claims are likely to be directed to HMOS, physicians, insurers, and employer-insurers. . . . We would encourage consideration of the view that the relevant audience for any claim should play a central role in identifying the claims made and assessing whether those claims are likely to be deceptive to that audience."

This is not new to FDA, of course. Courts have repeatedly held that compliance with section 502(a) should be judged by the meaning of the words to the audience to which the labeling is directed. United States v.23. More or Less, Articles, 192 F.2d 308, (2d. Cir. 195 1); V. E. Irons v. U. S., 244 F.2d 34 (1st. Cir. 1957), cert. denied 354 U.S. 923 (1957); U.S. v. Vrilium Products Co., 1938-1964 F.D.L.I. Jud. Rec. 944 (N.D. Ill. 1950), affirmed 185 F.2d. 3 (7th Cir. 1950). In line with that test, courts have interpreted section 502(a) as imposing a higher burden for substantiation when the audience is unsophisticated. E.g., United States v. Ten Cartons, More or Less, 1938-64 F. D.L.I. Jud. Rec. 1519 (1957); United States v. Hoxsey Cancer Clinic, 198 F.2d 273 (5th Cir. 1952); United States v. Vitamin Industries. Inc., 130 F. Supp. 755 (D. Neb. 1955); United States v. Articles of Drug . . . "Vit-RA-Tox", 263 F. Supp. 212, (D. Neb. 1967). The converse is also true--the more expert the audience, the lower the burden.

III. Guidance.

Under section 114 of the FDAMA, FDA will review promotional materials comprising HCEI that are disseminated or otherwise presented to decision-makers who select drugs for managed care and similar health benefits organizations to determine whether those materials are false or misleading under a competent and reliable scientific evidence standard. Promotional materials comprising other clinical information will be reviewed under the traditional standard for substantiation of promotional claims—i.e., the substantial evidence standard,

A. Competent And Reliable Scientific Evidence.

This is a flexible standard for assessing the adequacy of substantiation of HCEI considering: (1) what claims are made by the HCEI and in what form the information is disseminated, (2) who is the audience, and (3) whether there is a reasonable basis to substantiate the HCEI associated with a labeled indication as determined by the availability of competent and reliable scientific evidence.

If the substantiation for HCEI is stated expressly as part of the information, the firm must have at least the stated level of substantiation. If the HCEI is inconsistent with the substantial body of competent and reliable evidence in the area, the firm must have an adequate

explanation as to why the HCEI is considered to be competent and reliable. For example, without an adequate explanation, HCEI relying solely on the results of one small study would not be substantiated by competent and reliable scientific evidence if those findings are contradictory to results found in a large number of large well-designed studies. On the other hand, a single well-designed and conducted study that is directly related to an approved indication could provide competent and reliable substantiation for HCEI in the face of contrary evidence from poorly designed studies.

Where the substantiation for the HCEI is not stated expressly as part of the information, the following factors would be considered to determine whether there was competent and reliable scientific evidence to support the HCEI:

- Type of claim:—e.g., cost savings, cost-effectiveness, other forms of economic measure
- Nature of the product: —i.e., the condition for which a drug is used or the setting in which it is provided or used.
- Consequences of a false claim: —e.g., the degree of economic harm.
- Benefits of a truthful claim: —e.g., more informed decision making by those who must make decisions in real time in an uncontrolled world.
- Cost to develop different levels of substantiation for the claim: --consideration of technical and economic feasibility of conducting additional studies to substantiate the HCEI (cost, length of study, burden on patients, difficulty

with enrollment after efficacy has been demonstrated by well-controlled trials) balanced against the benefit of obtaining additional information to substantiate the claim (timeliness, relevance, significance).

. Amount of substantiation experts in the field believe is reasonable: --whether the information 'was developed and reported consistent with accepted guidelines on the conduct of health care economic studies. A number of guidelines have been published describing accepted practices for the conduct and reporting of HCEI. Although each guideline differs in some aspect from the others, many of the recommended practices are in concert. (For a summary of published guidelines, see, e.g., DeVries A, Gagnon JP. Cost effectiveness evaluation in health care: Initiatives for a standardized methodology. Managed Care Med. Feb. 1995 ;25-39. Genduso LA, Kotsanos JG. Review of health economic guidelines in the form of regulations, principles, policies, and positions. Drug Inform J. 1996; 30: 1003 -1016.)

Data obtained under a number of different study methods may be appropriate to provide substantiation for HCEI under the competent and reliable scientific evidence standard. These methods may include adequate and well-controlled experimental study designs but also may include observational study designs, such as case-control or cohort studies or other retrospective, prospective, or cross-sectional epidemiological studies, modeling techniques, and biometric approaches to synthesizing results from an evidence base.

As HCEI is generated using methods from a relatively young and dynamic discipline, it would not be appropriate to prescribe which methods for obtaining HCEI would be acceptable under a competent and reliable scientific evidence standard. Taking such a prescriptive approach in this guidance at this time could stifle methodologic advances in health care economics and ultimately could limit the flow of HCEI contrary to Congress's intent. Therefore, this guidance focuses on compliance with accepted guidelines for designing, conducting, and reporting findings from health care economic studies, such as those cited above.

B. Disclosure

Under section 114, FDA will focus on disclosure of material inputs and methods—an important feature of essentially all accepted guidelines in this discipline—to determine whether HCEI associated with an indication is substantiated by competent and reliable scientific evidence. While many forms of disclosure are appropriate, there are consensus approaches such as the one recommended by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) that include useful disclosures and/or disclaimers, See "Pharrnacoeconomic Modeling Disclaimer Proposed by ISPOR Panel", The "Pink Sheet", p. 8 (March 3, 1998). While health care economic information under section 114 is for promotional presentation, the ISPOR approach recommends the use of a standard disclaimer of limitations in any presentation of HCEI including journal articles and other scientific and commercial presentations based on models which rely on assumptions about a drug's efficacy.

The ISPOR approach is in harmony with the approach the agency has used in similar situations such as its "Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data," and "Guidance for Industry Funded Dissemination of Reference Texts." 61 Fed. Reg. 52800 (October 8, 1996). In its reprint guidance, FDA suggests that if a reprint contains effectiveness rates, data, analyses, uses, regimens or other information that is different from the approved labeling, the reprint should prominently state the difference(s), with specificity, on the face of the article. In addition, the guidance observes that the reprint should disclose all material facts.

The disclosure should provide information to explain the inputs, assumptions and methods made in the HCEI. Such disclosure should follow a standardized format and allow one reviewing the HCEI to determine the reliability and validity of the information and its relevance to decision making about allocation of resources. Standard formats for evaluating HCEI and underlying clinical information include those described by Stoddart and Drummond (Stoddart GL, Drurnmond MF. How to read clinical journals: VII. To understand an economic evaluation [parts A and B]. Can Med Assoc J. 1984; 130:1428-1434;1542-1549.), Naylor and Guyatt (Naylor CD, Guyatt GH. Users' guides to the medical literature. X. How to use an article reporting variations in the outcomes of health services. JAMA. 1996;275 :554-558.), and others.

Based upon those guidelines, one should consider disclosure of the following:

1. Identification of the research question which the HCEI is addressing.

2. Description of the alternatives considered in the HCEI.

3. The evidence used to establish the outcomes of each intervention or program included in the HCEI including disclosure of the type of evidence available ('g., meta-analysis of randomized controlled trials, single randomized controlled trial, clinical studies without randomization, observational and other nonexperimental methods, administrative data, expert opinion) and any extrapolations or linkages made from endpoints included in clinical trials to endpoints reported in the HCEI.

4. Identification of the costs and consequences for each alternative included in the HCEI including the perspective(s) considered, measurements of costs and outcomes in physical units (i.e., prior to valuation), and sources used to value costs and clinical outcomes.

5. Whether discounting was used for costs and clinical outcomes and the discount rate(s) used.

6. Whether results represent marginal (incremental) costs and outcomes.

7. Whether sensitivity analyses were performed and justification for ranges of values used in those analyses.

8. Bases for conclusions reached including generalizability of results to other settings and patient groups.

This disclosure should be placed prominently and in the front of any document containing HCEI.

C. Directly Related To An Approved Indication.

In addition to fitting within the parameters of the term HCEI, section 114 further limits the types of messages that would qualify for this special treatment to include only information that is directly related to an indication approved by FDA for inclusion in the drug's labeling. In particular, amended section 502(a) states that HCEI "shall not be considered to be false or misleading under this paragraph if the health care economic information directly relates to an indication approved under section 505 or under section 351(a) of the Public Health Service Act for such drug... ," Five examples are provided by the House Report (H.R. Rep. No. 105-310, pp. 65-66). These examples are meant to be illustrative, but not comprehensive nor restrictive.

Although managed care decision-makers may commonly consider the inclusion on formulary of off-label uses of approved drugs, section 114 does not authorize dissemination by manufacturers of promotional information related to those uses even under the less restrictive evidentiary standard of that section. Section 114 is limited to approved indications--i.e. those uses of an approved drug that involve conditions included in the approved labeling.

Examples of statements that are directly related to the approved labeled indication include, in certain cases, statements based on data involving practice settings, dosage levels actually used or prescribed, and durations of use that go beyond specific statements about those settings, dosages or durations of treatment included in the approved labeling. For example, if the labeling summarizes the results of a clinical trial conducted in a fee-for-service setting, HCEI extrapolating those findings to a managed care organization or other similar provider setting

could be directly related to the approved indication. If the approved labeling indicates a particular dosage for a drug and HCEI based upon drug utilization from a managed care organization database or a database from another provider setting includes actual patient use of the drug that may fall outside the approved dosage level, the HCEI could be directly related to the approved indication. (Drug utilization data provides the actual use of the drug, therefore, patients prescribed 25 mg of a drug bid which is labelled to be taken as 50 mg qd, may actually take 50 mg qd, 25 mg bid, 25 mg qd or O mg qd, and therefore, over the period covered by the DUR the daily dosage maybe something other than 50 mg qd as labelled.) In this case, it may be acceptable to use drug utilization databases for HCEI. If the approved labeling summarizes the results of a clinical trial in which the clinical endpoints were assessed following 6 months of treatment, HCEI based upon competent and reliable scientific evidence covering a duration of use beyond 6 months consistent with the labeled indication could be directly related to the approved indication.

D. Health Care Economic Information.

Under section 114, HCEI "means any analysis that identifies, measures or compares the economic consequences, including the costs of the represented health outcomes, of the use of a drug to the use of another drug, to another health care intervention or to no intervention." This definition includes all forms of economic analysis intended to facilitate decision making about the allocation of resources. Commonly used methods include, but are not limited to, cost analyses (also termed cost-consequence analyses, cost-identification analyses, or

cost-minimization analyses), cost-effectiveness analyses(including cost-utility analyses) and cost-benefit analyses.

HCEI comprises the report of an economic analysis including, as may be appropriate for a given analysis, a description of clinical and economic inputs, analysis methods, and findings. Clinical outcomes for which economic consequences may be presented in the HCEI associated with an approved indication may include physiologic, anatomic and biologic endpoints (e.g., blood pressure levels, survival rates, survival times, life expectancy, rates of myocardial infarction or stroke), health status and quality of life measures, quality adjusted life expectancy, measures of patient preference or satisfaction, or other measures relevant to decision makers.

Information on the burden of a disease (also called a burden of illness study ordinarily does not fall under the scope of the Act because ordinarily it is not labeling or advertising. Nevertheless, when burden-of-illness data does comprise advertising or labeling, FDA reviews the data to determine whether or not the data are truthful and not misleading using the competent and reliable scientific evidence standard.

Although HCEI is generally comparative in nature, information on the economic consequences of the use of a drug that is presented without comparison to another drug, another health care intervention or to no intervention would also be reviewed under the competent and reliable scientific evidence standard.

HCEI, which is disseminated to formulary or similar committees under section 114, may be disseminated in any of many forms. These include, but are not limited to, reprints of publications from peer reviewed journals, reports of proceedings from symposia, monographs, white' papers, sections from textbooks, print or broadcast advertisements, electronic media (software and interactive media), formulary kits, and presentation materials submitted to technology assessment panels, medical advisory boards, and formulary or pharmacy and therapeutics committees.

E. Formulary Committee or Similar Entity.

This clause should be read together with the next clause: "in the course of the committee or the entity carrying out its responsibilities for the selection of drugs" to refer to any entity that has a decision making role for selection of drugs or that advises those decision-makers. This may include a formulary committee, a pharmacy and therapeutics committee, a medical advisory board, technology assessment panel, or an individual, such as a medical director, provided that person or entity is responsible for the selection of drugs that maybe used in a group of patients (i.e., a decision-maker selecting drugs outside a one-on-one prescribing decision by an individual physician for an individual patient) or advises decision-makers who have such responsibility.

Section 114 reflects Congress's assessment that these entities have sufficient expertise to evaluate HCEI. Sponsors disseminating HCEI are not required to assess the expertise of their target audiences in understanding HCEI.

F. Managed Care or Other Similar Organization.

This would include health maintenance organizations, preferred provider organizations, point of service plans, managed indemnity plans, independent practice associations, integrated delivery systems (including hospitals), provider sponsored organizations, pharmacy benefit management organizations and other organizations that are involved with decision making about the coverage or payment for items or services provided to patients or that are at financial risk for care provided to patients or that are responsible for the allocation of health care resources including the selection of drugs and other treatments patients may be offered.

G. Submission Process for Health Care Economic Information.

As section 114 of the FDAMA only covers promotional use of HCEI, the process for submission of HCEI is no different from that for submission of other promotional materials (i.e., as required under 21 C.F.R.§ 314.81(b)(3)(i)). Prior approval is not required under Sec. 114 of FDAMA or FFDCA Sec. 502.

The submission should include the presentation of the HCEI in the form in which the information is to be disseminated (e.g., reprint of a publication from a peer-reviewed journal,

software package comprising an economic model with user manual) including package insert information, if required.

H. FDA Assessment.

FDA will review the HCEI under the competent and reliable scientific evidence standard as described above. In general, where FDA finds that HCEI may not meet the competent and reliable scientific evidence standard, before issuing a violation, the agency will contact the sponsor to obtain additional information about the evidence substantiating the HCEI and the audience to which it was disseminated. If after review of the substantiating information available, FDA still concludes that the HCEI is not supported by competent and reliable scientific evidence, the agency will work with the sponsor to determine whether the information can meet the competent and reliable scientific evidence standard if the information were amended or modified in some respect, including where appropriate, through the addition of a statement of limitations or qualifications to the information.

If after review, FDA finds that HCEI may not meet the competent and reliable scientific evidence standard, it may consider appropriate consultation with experts in the disciplines comprising health economics to assess whether the HCEI has that level of substantiation which experts in the field believe is reasonable. Such consultation would be made consistent with established rules limiting disclosure of proprietary information and in compliance with relevant administrative laws and procedures.